Newer Methods of Antimicrobial Delivery for Bone and Joint Infections

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Abstract
The advantages of systemic therapy include the ability to deliver antibiotics to areas that cannot be reached with topical therapy, the choice of a large selection of agents directed against the pathogens encountered in orthopaedic infections, and arrest or eradication of infection in most cases (in conjunction with adequate débridement). Disadvantages include the potential for toxicity from systemic agents, difficulty in achieving high concentrations of antimicrobial agents at the site of infection, and problems with compliance. To combat these disadvantages, newer methods for the delivery of antimicrobial agents have been investigated. Some of these newer methods include new formulations of antimicrobial agents to decrease systemic toxicity and improved methods for delivering local antimicrobial therapy.

Antibiotic Selection
In order to select the appropriate antibiotic(s), an understanding of the microbiology of open fracture wounds is imperative. Because open fractures are contaminated with both gram-positive and gram-negative organisms, antimicrobial therapy must be effective against both types of pathogens.

Factors related to antibiotic therapy that should be considered include the choice of antibiotic(s) and whether single versus combination therapy should be given, the duration of antimicrobial therapy, and the use of an antibiotic bead pouch (discussed later in this chapter).

Antibiotics
The first prospective study on open fractures and the first study in which a cephalosporin was used in the management of open fracture wounds was published in 1974. Three groups were studied: the patient group receiving no antibiotics had an infection rate of 13.9% (11 infections in 79 open fracture wounds), those with open fracture wounds who received penicillin and streptomycin had a 9.7% infection rate (9 infections in 92 open fracture wounds), and those who received cephalothin (a first-generation cephalosporin) had an infection rate of 2.3% (2 infections in 84 open fracture wounds).

Some investigators have recommended use of a single antimicrobial agent, such as a cephalosporin, for treatment of Gustilo-Anderson type I and type II open fracture wounds. However, this regimen would cover gram-positive contamination only. In addition, difficulty in classifying open fractures remains an issue even among the more experienced surgeons. Therefore, a Gustilo-Anderson...
type I or II open fracture wound, when treated with a single agent such as a first-generation cephalosporin, is ineffective against gram-negative contamination; this may actually be a misclassified type IIIA open fracture wound. Again, if a single agent is used, it must be effective against both gram-positive and gram-negative organisms.

Combination antibiotic therapy can consist of a first-generation cephalosporin with an aminoglycoside. For injuries sustained on a farm or in a stable, or vascular injuries, for which the presence of anaerobic organisms is likely, ampicillin or penicillin should be added to the regimen.

In a study by Sorger and associates, a comparison of gentamicin dosing (one dose of 6 mg/kg per day versus two doses of 5 mg/kg per day) revealed no difference in the infection rate. Moreover, single dosing was safe and effective. However, when an aminoglycoside is locally delivered with an antibiotic bead pouch, it is believed that systemic administration of an aminoglycoside is not needed.

Other antibiotics, including quinolones and aztreonam, may be used in combination with a cephalosporin to provide coverage for gram-negative organisms. In a double-blind prospective study of 171 open fractures, one group of patients received ciprofloxacin alone; another group received cefamandole and gentamicin. In type I and II open fracture wounds, an infection rate of 5.8% was reported for the ciprofloxacin group, and a 6% infection rate for the cefamandole/gentamicin group. In the type III open fracture wounds, 8 of 26 wounds (31%) became infected in the ciprofloxacin group versus 2 of 26 wounds (7.7%) in the cefamandole/gentamicin group. No significant difference in the infection rate between type I and II groups was reported, but there was a high failure rate for treating type III open fractures with ciprofloxacin alone, with infection being 5.33 times more likely to occur than with combination therapy.

Although these results were not statistically significant \( P = 0.079 \) because of the small sample size, there was a definite trend toward statistical significance.

In type III open fracture wounds, fluoroquinolones can be used in combination therapy, specifically as an alternative to an aminoglycoside. In type I and II open fracture wounds, however, they can be used as a single agent. In a study on open fracture wounds that occurred as a result of low-velocity gunshot injuries, oral ciprofloxacin reportedly was as effective as intravenous cephalosporin/aminoglycoside.

Quinolones, in addition to offering broad-spectrum antimicrobial coverage, can be administered orally at less frequent dosing than cephalosporins or aminoglycosides. Experimental studies, however, have suggested inhibition of osteoblasts and compromised fracture healing. Therefore, additional studies are needed to clarify the role of these antibiotics in the clinical setting.

Duration of Therapy
The length of therapy required for open fracture wounds is a controversial issue, with results from some studies showing no difference in open fracture infection rates treated for 1 day versus 5 days, whereas in other studies, treatment for a minimum of 3 days is recommended. Although the length of therapy is arbitrary, 3 days for open fracture wounds has been recommended to allow for complete culture results and for the wound to declare itself. Whenever a secondary major procedure, such as a soft-tissue muscle transfer, bone grafting, or internal fixation is being planned, additional antibiotics should be administered for 3 days based on initial culture results.

Newer Methods of Systemic Antimicrobial Delivery
One of the drawbacks to systemic antimicrobial therapy is the possibility of drug-related toxicity. Certain drugs, such as the penicillins and the cephalosporins, have a relatively low incidence of adverse effects and can be used at the high doses needed to reach a high local concentration at the site of infection. Other drugs, such as the aminoglycosides, have significant, dose-limiting, adverse effects that restrict their use in many instances.

New systemic antimicrobial delivery systems have been investigated to decrease toxicity and increase the concentration of drug at the target site. The incorporation of a drug into a liposome, a lipid bilayer micelle, may achieve that goal. In the United States, a commercial preparation of amphotericin B in a liposome (AmBisome, Fujisawa, Deerfield, IL) has been approved by the US Food and Drug Administration (FDA). This preparation appears to have less nephrotoxicity than the standard preparation of amphotericin B and has similar or greater efficacy.

Although fungal infections are rare in orthopaedics, a similar approach to systemic antimicrobial delivery has been tried with the aminoglycosides. Gentamicin, tobramycin, and amikacin, all have been incorporated into liposomes and studied in vitro and animal models. The efficacy of these preparations, especially against gram-negative organisms such as Pseudomonas aeruginosa, appears to be as great or greater than that of standard aminoglycoside preparations. Additional studies will be needed to assess their toxicity.

Local Antimicrobial Therapy
Antibiotic-Impregnated Polymethylmethacrylate Cement Beads
Because of the drawbacks associated with systemic antimicrobial therapy, the use of local therapy has been investigated. Buchholz and Engelbrecht in 1970 proposed delivering antibiotics to an infected site via elution of antibiotics from antibiotic-impregnated cement placed adjacent to the site of infection. 
late (PMMA) cement beads for the treatment of orthopaedic infections has many theoretical advantages. The beads, which release antibiotics by passive diffusion, combine high local concentrations with low systemic levels of the antibiotic, leading to more effective killing of the organism and less risk of systemic toxicity. In addition, the beads can fill the dead space that may be left after débridement of infected tissue. Compliance with taking medication is not an issue when beads are used for antibiotic delivery.

There have been many in vitro studies on the diffusion or elution of antibiotics from PMMA cement. Several different antimicrobial agents have been studied, including the aminoglycosides (primarily gentamicin, but also tobramycin, amikacin, and streptomycin), cephalosporins (including cefazolin, cefotaxime, ceftriaxone, and ceftazidime), vancomycin, and fluconazole. All antimicrobial agents go through an initial phase during which the concentration of fluid surrounding the beads is very high, followed by a gradual decrease to sustained low levels for many weeks or months. Although there are differences in elution between each different antimicrobial agent, all seem to have adequate elution for the treatment of infection, but the length of time that the drug levels remain above the minimum inhibitory concentration for the target organism (usually Staphylococcus aureus) varies depending on the drug selected and the conditions of the experiment.

Several factors influence the elution of antibiotics from PMMA cement. In addition to the type of antibiotic used, the type of cement also influences elution. Factors that increase the porosity of the cement (such as the addition of dextran or higher concentrations of antibiotic) also increase elution. Walenkamp showed that the size of the bead influenced the amount of antibiotic that can be eluted. Small or mini beads provide better elution than larger beads, probably because of a more favorable surface to volume ratio. Finally, the turnover of the fluid surrounding the beads will influence the local concentration as well as the maximum amount of antibiotic eluted.

The efficacy of antibiotic-impregnated beads in the treatment of osteomyelitis has been examined in several animal model studies. In a 1972 study, Klemm reported on the results of the treatment in patients with osteomyelitis using gentamicin-impregnated cement beads. Many uncontrolled studies in the medical literature over the last three decades have reported a good outcome in patients treated with beads alone or beads combined with systemic therapy.

Although the use of antibiotic-impregnated PMMA cement beads is becoming more widespread, only four unique, truly randomized, controlled clinical trials have been published that compare treatment outcome using beads with conventional systemic therapy. In one of these studies on the treatment of open fractures (Gustilo-Anderson types II, IIIA, and IIIB), no difference in outcome was noted between those treated with tobramycin-impregnated beads and those treated with intravenous antibiotics. In the second study, done in 1980, the use of gentamicin-impregnated beads was compared with suction-irrigation drainage in patients with chronic osteomyelitis; no difference in outcome was found. In the third study, the use of gentamicin-impregnated beads and intravenous antibiotic therapy was compared with intravenous antibiotic therapy alone in treating infected nonunions; again, no difference in outcome was found. Patients with infected total hip and knee arthroplasties treated with parenteral antibiotics with or without gentamicin-impregnated bead implantation were evaluated in the fourth study; again, no significant difference in outcome was noted. All of these studies had small patient groups (n ≤ 55).

In Germany, gentamicin-impregnated PMMA beads are commercially available under the product name Septopal (E. Merck, Darmstadt, Germany). However, the FDA has not approved a commercial product, so all use of antibiotic-impregnated beads in the United States is off-label. The beads can be individually manufactured by the surgeon for implantation using commercially available PMMA cement mixed with a powdered antibiotic, or can be created with the assistance of an individually-made bead mold. The elution characteristics of physician-made beads are less predictable than those of the commercially manufactured (Septopal) beads; therefore, the results from Europe regarding the Septopal beads may not be applicable in the United States.

With physician-manufactured beads, the type of antimicrobial agent to incorporate into the cement and the amount to use are choices that should be considered. Certain antimicrobial agents such as gentamicin, amikacin, and clindamycin cannot be used because they are not available in the United States in a sterile powdered form. If the infecting organism is known, the drug chosen should demonstrate activity against that organism. Otherwise, empiric choices of drugs should cover common organisms such as S. aureus and coagulase-negative staphylococci. Common choices are tobramycin (although there are areas where significant staphylococcal resistance to tobramycin is seen), vancomycin, and some of the cephalosporins. Although the optimal concentration of antibiotic in cement is not known, the usual amounts used are provided in Table 1.

Although there are many advantages associated with using antibiotic-impregnated PMMA beads, there are several disadvantages as well. As mentioned previously, certain antibiotics are not available in the United States in sterile powdered form and thus cannot be used. The beads provide a high local concentration of antibiotic with a low systemic serum.
level, but if high concentrations are used in cement or if several bags of antibiotic-impregnated cement are placed in the wound, systemic toxicity may result. For beads left in place for many weeks, there is a concern that long exposure to subtherapeutic levels of antibiotics may lead to the development of resistant organisms, especially with the use of vancomycin. Finally, the beads themselves may act as foreign bodies after the elution of antibiotics is completed, necessitating their removal.

In patients with infected total joint arthroplasties, PMMA beads may deliver antibiotics to the area of infection yet not adequately fill the dead space. Blocks or spacers made of antibiotic-impregnated PMMA cement or metal prostheses covered with antibiotic-impregnated PMMA cement have been created to fill the dead space.

**Biodegradable Vehicles**

In order to address some of the drawbacks of local antibiotic delivery with antibiotic-impregnated PMMA cement, the use of biodegradable vehicles for the delivery of antibiotics has been studied. Unlike PMMA beads, these biodegradable beads deliver high levels of local antibiotics without significant systemic levels. In addition, these biodegradable beads deliver antibiotics for a prolonged period.

Unlike PMMA beads, however, these new materials will biodegrade (or bioerode) and thus not remain as a foreign body. Thus, there is no need for additional surgery to remove these beads. Another advantage is that, depending on the manufacturing process, many different antibiotics could be incorporated into the biodegradable beads, thus overcoming some of the limitations in the choice of antibiotics that currently restrict the physician-made PMMA beads.

Many different materials have been tried in vitro and in vivo as possible methods of antibiotic therapy, including plaster of Paris in 1982. Since then, trials with many other materials have been done, including lactic acid oligomer, calcium sulfate, polyglycolic acid, polylactide-polyglycolide copolymers, poly(l-lactide), polylactic acid and poly (DL-lactide)-co-glycolide, polyanhydrides, and lactide-polyglycolide copolymers, poly(L-lactide), polylactic acid and poly (DL-lactide):co-glycolide, polyanhydroxides, and fibrin clots. Currently, to our knowledge, no large human trials have been published and none of these materials has been approved for antibiotic delivery by the FDA.

**Summary**

The appropriate use of antimicrobial agents has decreased morbidity and mortality from orthopaedic-related infections. Although systemic antibiotic use has been used for many years, new methods of local antibiotic delivery may result in increased antibiotic levels, decreased toxicity, and possibly greater efficacy. Antibiotic-impregnated PMMA beads are currently being used in a variety of applications. New research directions include the development of new, biodegradable materials for the delivery of local antibiotics and further clinical trials to clarify the optimal use of these delivery systems.

**References**

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